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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/305,084	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 43-59 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 43-59 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 33-42 have been canceled. Claims 43-59 have been added and are under consideration.

Claims 56 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 56 and 57 recite "wherein the patient displays one or more atypical moles". It is unclear how this limitation further limits the scope of claims 43 and 45 because a patient in need of treatment for melanoma would have at least one atypical mole.

Claim 43 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the selective antagonization of the ETB receptor in a patient having melanoma comprising the administration of known peptide antagonists of ET(B) receptor and antibodies which antagonize the ET(B) receptor, does not reasonably provide enablement for selectively antagonizing the ET(B) receptor by means involving the administration of . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following reasons of record were set forth on page 5-7 of the Office action of March 15, 2004.

(B)As drawn to the treatment of cancers by anti-sense therapy

The claims are drawn in part to a method of inhibiting cancer comprising the administration of an ETB antisense molecule. The specification contemplates this application as gene therapy (section 5.3, pages 26-27). The specification does not reasonably provide enablement for the administration of an ETB antisense molecule or a ribozyme targeting the ETB receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and us the invention commensurate in scope with these claims.

In order to practice the full scope of the claims, the medical procedure of gene therapy must be enabled. However, the state of the art as of the priority date sought for the instant

application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), . Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that data regarding the level and consistency of

expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claim 26 to the extent that it reads on gene therapy.

Claims 43-46, 50, 53 and 56-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739, reference of the IDS filed February 8, 2001) in view of Vournakis et al (U.S. 6,063,911, cited in a previous Office action).

Vournakis et al teach a method of treating cancers comprising the administration of an endothelin agonist in combination with poly-N-acetylglucosamine (column 1, lines 15-30). Vournakis et al teach that melanoma is one of the few tumors to express ETB receptor that have an affinity for all three isoforms of endothelin and that said ETB receptors are expressed in primary and recurrent melanoma but the expression of ETB is decreased in metastatic melanoma (column 2, lines 46-53). Vournakis et al teach that the ETA antagonist, Ro61, inhibited melanoma proliferation in vitro (column 4, lines 45-46), and that that Ro61 is a non-specific inhibitor of both endothelin receptors, ETA and ETB (column 3, lines 44-46). Vournakis et al teach that the endothelin antagonist of BQ788 is included with the endothelin antagonists in the compositions of the invention (column 17, lines 9-19). Vournakis et al teach that a target for the poly-N-acetylglucosamine compositions of the invention is the skin (column 22, lines 59-61). Vournakis et al teach that poly-N-acetylglucosamine in combination with Ro61 delayed the death of mice carrying transplanted B16 melanoma cells and caused the complete regression of the melanoma cells in 33% of the animals after tumor injection (column 32, lines 32-41).

Vournakis et al to not teach the treatment of melanoma with poly-N-acetylglucosamine and the ETB specific antagonist of BQ788.

Kikuchi et al teach the inhibition of proliferation in primary melanoma cell lines by BQ788 (page 735 to 736, bridging sentence. Kikuchi et al teach that levels of the ETB receptor are decreased in metastatic melanoma cell lines (Table 2).

It would have been prima facie obvious at the time the invention was made to combine the ETB antagonist of BQ788 with poly-N-acetylglucosamine for the treatment of primary melanoma. One of skill in the art would have been motivated to do so by the teachings Kikuchi et al on the inhibition of primary melanoma cells lines by BQ788 and the teachings of Vournakis on targeting the poly-N-acetylglucosamine/ endothelin receptor antagonists to the skin, as well as the demonstration by Vournakis et al that Ro61 which is an antagonist for either the ETA or ETB receptor was able to inhibit the proliferation of melanoma cells. One of skill in the art would understand that the Ro61 antagonist could act through either the ETB or ETA receptors, and therefore in light of the teachings of Kikuchi et al would understand that ETB could be substituted for Ro61 in the poly-N-acetylglucosamine composition for the treatment of melanoma in a patient in need thereof. Claims 58 and 59 are included with this rejection because they are product by process claims for the characterization of the ET(B) antagonists. The structure and properties of BQ 788 fulfill the specific embodiments of claims 58 and 59.

Applicant has submitted the Declaration under 37 C.R.F. 1.131 of both of the instant inventors in order to aver that the instant invention was conceived before December 22, 1998 and that said inventors were engaged in reducing the conception into practice before December 22, 1998. The Declaration has been carefully reviewed but considered to be defective. 37 CFR 1.131 states that

Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country.

The instant Declaration fails to state the country in which the invention was established prior to December 22, 1998 and thus is ineffective to overcome the reference of Vournakis et al (U.S. 6,063,911).

Claims 43-46, 48, 50, 53 and 56-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739).

Kikuchi et al teach that contacting of BQ-788, a ETB antagonist with a primary melanoma cell line , PM-WK, which expresses high level of ETB receptors resulted in a significant decrease in the mitogenic activity stimulated by the ET-1 or ET-3 , but that contacting with BQ-123 had no such effect (page 735, line 1 to page 746, line 2). Kikuchi et al teach that the ETB receptor subtype mainly initiates mitogenic signaling in primary melanoma (page 738, lines 6-8).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer BQ-788 to a patient having a primary melanoma expressing the ETB receptor, or a recurrent melanoma expressing the ETB receptor. One of skill in the art would have been motivated to do so by the teachings of Kikuchi et al on the ability of BQ-788 to inhibit the growth of melanoma cells expressing the ETB receptor in the presence of ET-1 and ET-3 and the teachings of Nelson et al on the ability of BQ788 to bind to ETB receptors when administered in vivo. One of skill in the art would reasonably conclude that BQ788 would bind and antagonize the ETB receptor on primary or recurrent melanoma cells in vivo even in the presence of the endogenous ET-1 and ET-3 ligands. Claims 58 and 59 are included with this rejection because they are product by process claims for the characterization of the ET(b) antagonists. The structure and properties of BQ 788 fulfill the specific embodiments of claims 58 and 59.

Applicant has previously argued in the Response of August 12, 2004 that Kikuchi et l fails to demonstrate actual melanoma cell proliferation in response to ET-1, and that Kikuchi actually teaches away from the instant invention in light of the teachings regarding metastatic melanoma. Applicant argues that Kikuchi's conclusion that "mitogenic effects of endothelin in

human primary melanoma are mainly mediated through ETB receptors" is not convincing in light of the lack of connection between ET and cancer progression or a link between ET signaling and pre-metastatic events. Applicant concludes that a skilled artisan would not conclude that ETB might be involved in melanoma progression. This has been considered but not found persuasive. The instant claims are drawn to the treatment of melanoma. As such, efficacy of said treatment would be recognized by one of skill in the art to include decreasing tumor burden of the primary tumor, or causing disease stabilization of the primary tumor, and/or decreasing t invasiveness of the primary tumor, which is separate from inhibiting metastatic lesions. The claims do not require that the treatment be involved in pre-metastatic events because melanoma spreads by local invasion as well as by metastasis. One of skill in the art would conclude that deprivation of a mitogen would result in less mitosis in the primary lesion and a decrease in potential for local invasion.

Applicant argues that Kikuchi does not suggest that BQ 788 would prevent melanocytes for developing into melanoma cells. This is not persuasive for the reasons sated above, that the instant claims do not require the prevention of melanoma. Applicant alleges that Kikuchi does not show any effect of BQ-788 on cell proliferation

Applicant argues that Kikuchi does not show any effect of BQ-788 on cell proliferation. this has been considered but not found persuasive. Applicant is again referred to page 735, line 1 to page 746, line 2 of Kikuchi et al wherein it is stated that

Furthermore, we observed that BQ-788 (100 nM) significantly attenuated the increase in mitogenic activity stimulated by 100 nM ET-1 or ET-3 in PM-WK; while BQ-123 (100 nM) had no such effect.

Claims 43-46, 48, 50-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739) as applied to claims 43-46, 48, 50, 53 and 56-59 above, and further in view of Battistini et

al (Pulmonary Pharmacology and Therapeutics, 1998, Vol. 11, pp. 97-112, reference of the IDS submitted July 25, 2003).

Claims 51, 52, 54 and 55 specify the endothelin B antagonists of IRL-1038 and RES-701-1. Battistini et al teach that IRL-1038 and RES-701-1. as well as BQ 788 (page 100, Table 1).

It would have been prima facie obvious at the time the claimed invention was made to substitute IRL-1038 or RES-701-1 for the BQ 788 taught by Kikuchi et al. One of skill in the art would have been motivated to do so by the teachings of Kikuchi that the ETB receptor subtype mainly initiates mitogenic signaling in primary melanoma and the example wherein BQ 788 counteracts a mitogenic signal. One of skill in the art would understand that other ET(B) receptor antagonists in addition to BQ 788 would precipitate the same effect on primary melanoma.. Claims 58 and 59 are included with this rejection because they are product by process claims for the characterization of the ET(b) antagonists. The structure and properties of IRL-1038, RES-701-1, and BQ 788 fulfill the specific embodiments of claims 58 and 59.

Claims 43-50, 53 and 56-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739) as applied to claims 43-46, 48, 50, 53 and 56-59 above, and further in view of Ferrara et al (U.S. 5,573,762).

Ferrara et al teach that blockers of the endothelin B receptor includes antibodies (column 6, lines 15-17).

It would have been prima facie obvious at the time the claimed invention was made to substitute an anti-endothelin B antagonistic antibody for the BQ 788 taught by Kikuchi et al. One of skill in the art would have been motivated to do so by the teachings of Ferrara et al who suggest that antibodies can be used to block the endothelin B receptor and by the teachings of Kikuchi that the ETB receptor subtype mainly initiates mitogenic signaling in primary melanoma and the example wherein BQ 788 counteracts a mitogenic signal. One of skill in the art would understand that other ET(B) receptor antagonists in addition to BQ 788 would precipitate the same effect on primary melanoma.. Claims 58 and 59 are included with this rejection because they are product by process claims for the characterization of the ET(b)

antagonists. The structure of an antagonistic endothelin B antibody fulfills the specific embodiments of claims 58 and 59.

All claims are rejected.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
10/15/2006